

USE OF TROPHIC FACTORS IN PREVENTING PHYSICAL FRAILTY

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RFA: AG/AR 91-11

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National Institute On Aging

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Letter of Intent Receipt Date: November 1, 1991

Application Receipt Date: January 15, 1992

PURPOSE

The National Institute on Aging (NIA) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invite applications for explorations of the potential for use of trophic factors in the prevention of physical frailty among older persons. The acquisition of new knowledge concerning the effects of growth factors, anabolic hormones, and pharmacologic trophic agents on prevention and treatment of conditions responsible for impaired strength, mobility, balance, and endurance in older persons is the goal of this solicitation.

The role of growth factors, anabolic hormones and pharmacologic trophic agents in the prevention or treatment of conditions responsible for physical frailty (disabling impairments in strength, mobility, balance, and endurance) deserves increased attention. This field has progressed to the point where preliminary clinical studies are possible in many cases, in addition to continued basic studies. The recent report that growth hormone administration to healthy older men with low growth hormone levels increased lean body mass and decreased body fat illustrates this potential. An increasing number of growth stimulators and modulators are being identified that could be useful as replacement therapy in persons with deficient concentrations of these substances. They may also have value for administration in pharmacological doses to enhance desired effects in persons with normal serum concentrations but inadequate end organ responses. There is also great potential for pharmacologic agents and other interventions

that have direct trophic effects, stimulate endogenous production of trophic factors, or increase end organ responses to trophic factors.

The impact that such factors may have on increasing muscle strength and mobility, preventing osteoporosis and osteoarthritis, and improving the healing of fractures, leg ulcers, and decubiti are among the most promising benefits that may result and lead to significant improvements in the health of older persons. Severe muscle atrophy and weakness occur in many older people, decreasing their mobility and functional capacity and leading to falls, hip fractures, and loss of independence. Besides growth hormone, several other factors, including testosterone and certain pharmacologic adrenergic-agonists, might be useful in preventing or reversing muscle atrophy in certain older populations. In the prevention and treatment of osteoporosis and osteoarthritis, it may eventually be possible to manipulate levels of bone and cartilage growth factors and responses to them, as well as circulating hormones. Healing of wounds, pressure sores and other skin ulcers, and fractures is slow in many older patients, resulting in prolonged disability. Trophic factors may play a role in speeding these healing processes.

Because the frail older population has a very high proportion of women, there is a particular need to determine the effects of gender on the actions of trophic factors in older persons. In addition, more knowledge is needed on the role of ovarian hormonal replacement therapy in countering degenerative conditions responsible for frailty.

In addition to testing the effects of trophic factors on specific degenerative conditions, information is needed about the effects of trophic factors in particular clinical situations (e.g., to prevent weight loss during hospitalization).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and nonprofit, organizations, either public or private, such as universities, colleges, hospitals, laboratories, units of State or local governments, and eligible agencies of the Federal Government. Applications from minority individuals and women are encouraged.

MECHANISM OF SUPPORT

Support of this program will be through the Public Health Service grant-in-aid. Only the RO1 grant mechanism will be used. Awards will be administered under PHS grants policy as stated in the Public Health Service Grants Policy Statement, DHHS Publication No. (OASH) 90-50,000, revised October 1, 1990.

Generally, future unsolicited competing renewal applications will compete with all investigator-initiated applications and be reviewed by the Division of Research Grants. However, should the NIA determine that there is a sufficient continuing program need, the Request for Applications (RFA) will be reissued. The earliest feasible start date for the initial awards will be July 1, 1992.

FUNDS AVAILABLE

This RFA is a one-time solicitation. Up to \$2.5 million (total cost) for first-year expenses, and additional approved expenses for up to five years, will be committed to fund applications submitted in response to this RFA. This funding level is dependent on the receipt of a sufficient number of applications of high scientific merit. It is anticipated that approximately ten awards will be made. The NIAMS is expected to award up to \$500,000 for one or two applications that receive primary assignment to NIAMS.

RESEARCH OBJECTIVES

This RFA solicits research on the effects of trophic factors in preventing or reversing processes or conditions responsible for physical frailty. Inclusion of ancillary studies to determine mechanisms responsible for tissue responsiveness or nonresponsiveness is strongly encouraged. All proposals must include studies on human subjects, but additional laboratory animal studies or in vitro studies may also be included if appropriate (e.g., for tests not feasible in humans). Studies of potential adverse effects as well as therapeutic benefits are encouraged. Collaborative approaches including expertise in geriatrics, endocrinology, pharmacology, and other clinical and basic sciences, are encouraged. Studies should be carried out in carefully defined populations, with attention to the effects of age, gender, ethnicity, and specific diseases. Attention to functional as well as physiologic effects is encouraged.

Specific topics of interest include:

- o The role of replacement therapy with hormones and other trophic factors (such as growth hormone, IGF-1, testosterone, or estrogens) or pharmacologic agents that may prevent or reverse atrophic or dystrophic degenerative changes responsible for conditions such as osteoporosis, osteoarthritis, loss of muscle mass, and others.
- o Effects of interventions that may increase endogenous levels of trophic factors (e.g., administration of pharmacologic agents, pituitary or hypothalamic factors, or exercise and other lifestyle factors that may affect such parameters as production, localization, or circulating levels of trophic factors) in older persons.
- o Role of local tissue factors in modulating degenerative or atrophic changes in bone, muscle, and cartilage in older persons.
- o Studies on factors that may accelerate healing of wounds, fractures, pressure sores and other ulcerative skin conditions in older persons.
- o Effects of age-related physiologic changes and age-related diseases on responses to trophic factors, including studies of mechanisms mediating these effects.
- o Systemic effects of trophic factor administration (e.g., on cardiovascular function, metabolism, renal function, pulmonary function, immune function) in older persons.

SPECIAL REQUIREMENTS

The Principal Investigators of funded projects, under the terms of the awards, will meet with NIA staff yearly to review the progress of their studies and review possible needs and opportunities for multi-site trials. Funds for such travel must be requested in applications.

STUDY POPULATIONS

It is NIH policy that women and minorities must be included in clinical study populations unless there is a good reason to exclude them. The study design must seek to identify any pertinent gender or minority population differences.

SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF NIH POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDY POPULATIONS

NIH policy is that, as appropriate, applicants and offerors for NIH grants, cooperative agreements, and contracts will be required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the diseases, disorders, or conditions under study; special emphasis should be placed on the need for inclusion of minorities and women in studies of diseases, disorders, and conditions that disproportionately affect them. This policy is intended to apply to males as well as females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale for exception to the policy must be provided.

The composition of the proposed study population must be described in terms of gender and racial/ethnic groups, together with a rationale for its choice. In addition, gender and racial/ethnic issues should be addressed in developing a research design and sample size appropriate for the scientific objectives of the study. This information should be included in the form PHS 398 in Section 2, A-D of the Research Plan AND summarized in Section 2, E, Human Subjects.

Applicants are urged to assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH recognizes that it may not be feasible or appropriate in all research projects to include representation of the full array of United States racial/ethnic minority populations (i.e., Native Americans (including American Indians or Alaskan Natives, Asian/Pacific Islanders, Blacks, Hispanics). The rationale for studies on single minority populations should be provided. For the purpose of this policy, clinical research includes human biomedical and behavioral studies of etiology, diagnosis, or treatment of diseases, disorders or conditions, including but not limited to clinical trials.

The usual NIH policies concerning research on human subjects also apply. Basic research or clinical studies in which human tissues cannot be identified or linked to individuals are exempt. However, every effort should be made to include human tissues from women and racial/ethnic minorities when it is important to apply the results of the study broadly, and this should be addressed by applicants.

For foreign awards, the policy on inclusion of women applies fully; since the definition of minority differs in other countries, the applicant must discuss the relevance of research involving foreign population groups to the United States' populations, including minorities.

If the required information is not contained within the application, the application will be returned without review.

Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If the representation of women or minorities in a study is inadequate to answer the scientific questions(s) addressed and the justification for the selected study population is inadequate, it will be considered a scientific weakness or deficiency in the study design and will be reflected in assigning the priority score to the application. All applications for clinical research submitted to NIH are required to address these policies. NIH funding components will not award grants or cooperative agreements that do not comply with these policies.

REVIEW CONSIDERATIONS

Applications will be received by the NIH Division of Research Grants. The customary referral guidelines apply and some applications may be assigned to NIAMS. Applications will be assigned to an Institute/Center/Division (ICD) special review group for review. Applications judged by the ICD to be non-responsive (those not directed at the goals of this RFA) or that fail to comply with the instructions for completing form PHS 398 (rev. 10/88), will be administratively withdrawn and returned to the applicant without review. Applications involving the use of human subjects or vertebrate animals require review and approval by appropriate institutional committees. Applications not complying with this policy will be returned to the applicant without review. Those applications that are

complete and responsive will be evaluated in accordance with the criteria stated below for scientific/technical merit by an appropriate peer review group convened by the ICD. Applications may be subjected to triage by an ICD peer review group to determine their scientific merit relative to other applications received in response to this RFA. The NIH will withdraw from further competition those applications judged by triage to be noncompetitive for award and notify the applicant Principal Investigator and institutional official. Those applications judged to be competitive will undergo further scientific merit review. The second level of review will be provided by the assigned ICD Council/Board.

Listed below are the review criteria to be used in the evaluation of the applications received in response to this RFA:

- o scientific merit of the proposed research;
- o significance of the research project to the goals of the RFA;
- o qualifications, experience, and commitment of the investigators and their ability to devote the required time and effort to the project;
- o appropriateness of the total budget and budgetary requests;
- o institutional commitment to the requirements of the project.

APPLICATION PROCEDURES

Applications must be submitted on the PHS 398 application form (rev.10/88) that is available at most institutional business offices and from the Division of Research Grants, NIH, telephone (301) 496-7441. The deadline for receipt of applications is January 15, 1992.

On item 2 of the face page of the application, applicants must enter: RFA AG/AR-91-11 -- Potential of Trophic Factors for Preventing Physical Frailty. The RFA label available in the 10/88 revision of the application form PHS 398 must be affixed to the bottom of the face page and placed on top of the entire package. Failure to use this label could result in delayed processing of the application and

prevent it from reaching the review committee in time for review. The completed application and four copies must be sent to:

Application Receipt Office
Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

At the same time the application is submitted to the Division of Research Grants, two copies of the application must be sent to:

Chief, Scientific Review Office
National Institute on Aging
Building 31, Room 5C12
9000 Rockville Pike
Bethesda, MD 20892

Failure of these copies to be received by the deadline may prevent the application from being reviewed under this announcement in time to be considered for an award.

LETTER OF INTENT

A letter of intent to submit an application, while not required, is requested. This letter should be addressed to Stanley L. Slater, M.D. (address below). The letter of intent is to include a descriptive title, the name and address of the Principal Investigator and any other participating institutions.

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries for the NIA regarding programmatic issues to:

Stanley L. Slater, M.D.
Geriatrics Program
National Institutes of Health
National Institute on Aging
Building 31, Room 5C27
Bethesda, MD 20892
Telephone: (301) 496-6761

Direct inquiries for the NIAMS regarding programmatic issues to:

Dr. Stephen L. Gordon
National Institute of Arthritis and Musculoskeletal and Skin Diseases
5333 Westbard Avenue
Room 407
Bethesda, MD 20892
Telephone: (301) 496-7326

Direct inquiries for the NIA regarding fiscal matters to:

Barbara Cunningham
Grants and Contracts Management Office
National Institutes of Health
National Institute on Aging
Building 31, Room 5C07
Bethesda, MD 20892
Telephone: (301) 496-1472

Direct inquiries for the NIAMS regarding fiscal matters to:

Ms. G. Carol Clearfield
National Institute of Arthritis and Musculoskeletal and Skin Diseases
5333 Westbard Avenue
Room 403
Bethesda, MD 20892
Telephone: (301) 496-6529

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.866. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410), as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.